Remarks

Support for the Amendments Status of the Claims

By the foregoing amendments, claim 1 is sought to be amended. Support for the amendments to claim 1 can be found throughout the specification as-filed. Therefore, these amendments introduce no new matter.

Upon entry of the foregoing amendments, claims 1-16, 93-101, 106-107, 112-133, 138-159, 162, 164-165, 167, 169, 171, 173-175, 177, 181-186, 188 and 193-197 are pending in the application, with claim 1 being the sole independent claim.

Applicants note that, in the Office Action at page 2, the Examiner has indicated that claims 173-175, 177, 181-186, 188 and 192-195 are withdrawn from consideration. However, also at page 2, the Examiner indicates that claims 173, 174, 177, 181-186, 188 and 193-195 are currently under consideration, and in fact, the Examiner has rejected claims 173, 174, 177, 181-186, 188 and 193-195 throughout the Office Action. Applicants respectfully submit that claims 12-16, 93-101, 106-107, 112-133, 138-140, 142-159, 162, 165, 167, 171, 175 and 196-197 have been withdrawn from consideration by the Examiner, and have indicated the status of the claims as such. Applicants request that the Examiner confirm the withdrawn claims with the next Office Communication.

Summary of the Office Action

In the Office Action dated March 18, 2008, the Examiner has made five rejections of the claims. Applicants respectfully offer the following remarks to traverse

each of these elements of the Office Action. Applicants respectfully request reconsideration of the present Application.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

In the Office Action at pages 2-5, the Examiner has rejected claims 1-11, 141, 164, 169, 173, 174, 177, 178, 181-186, 188, 193-195 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner asserts that the term "comprises 61 kinases" is not supported in the as-filed specification. Applicants respectfully disagree with the Examiner.

In Applicants' previous Reply to Office Action filed December 21, 2007, the disclosure of which is incorporated by reference herein in its entirety, Applicants noted that in the present specification, Example 1 at pages 27-38, discloses the production of positionally addressable arrays comprising at least 122 yeast kinases. As previously stated, Applicants respectfully submit that the production of an array comprising 122 kinases clearly, must implicitly and inherently, encompass an array comprising 61 kinases. Furthermore, Applicants note the specification at page 11, lines 14-19, discloses the use of 50%, 75%, 90% or 95% of all of the expressed proteins with same type of biological activity in the genome of an organism. A person of ordinary skill in the art would readily recognize that 50% of 122 kinases is equal to 61 kinases, as recited in present claim 1.

Applicants again submit that *in haec verba* support is not necessitated by the written description requirement of 35 U.S.C. § 112, first paragraph, and that newly added

claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *See* M.P.E.P. § 2163(I)(B). Applicants note that the preparation of an array comprising 122 kinases must, at the very least implicitly and inherently, provide support for an array comprising 61 kinases (or any number between 1 and 122 inclusive, for that matter). Furthermore, disclosure of arrays comprising 50% of 122 kinases (i.e., 61 kinases) provides explicit support for the recitation of 61 kinases in present claim 1. Thus, a person of ordinary skill in the art would readily understand that Applicants were in full possession of the presently claimed invention at the time of filing.

In response to Applicants' arguments, the Examiner continues to assert that "[w]hether a limitation constitutes new matter is not whether one skilled in the art would know that 50% of 122 kinases is equal to 61 kinases, as recited in amended claimed 1. Rather, whether the newly added claim limitation of 61 kinases is present in the as-filed specification." Office Action at page 5, last paragraph. Furthermore, the Examiner asserts that "Example I, page 27 recites the 122 genes specifically from the yeast genome, not from the broad claimed any kinase from any type of organisms." *Id.* at first paragraph.

Applicants respectfully submit, as previously noted, a person of ordinary skill in the art would readily understand that indeed, Applicants were clearly in possession of a positionally addressable array comprising 61 purified active kinases or functional kinase domains thereof of a mammal, yeast or *Drosophila*. At page 26, lines 17-21 of the present specification, it is stated that "[i]n a specific embodiment, one or more protein chips in the kit have, attached to the wells of the solid support, at least 50%, 75%, 90% or 95% of all expressed kinases . . . within the genome of an organism." As previously

noted, as disclosed in Example 1, the present specification clearly provides written support for an array utilizing all 122 kinases of the yeast organism. Therefore, an array comprising 50% of these 122 kinases, as described at page 26 of the present specification, provides written description support for an array comprising 61 kinases. Concluding otherwise is not only incomprehensible, but contrary to written description case law.

Applicants note that, as the Federal Circuit has held, the written description requirement must be viewed in light of the state of the art at the time of filing. *Capon v. Eshhar*, 418 F.3d 1349, 1357-1358 (Fed Cir. 2005) ("[t]he descriptive text needed to meet these [written description] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence."). Furthermore, in *Capon*, the Federal Circuit stated that the Board's reliance on *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) and *Enzo Biochem Inc., v. GenProbe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002), for the case at bar was incorrect and explained that "[n]one of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., *Regents v. Lilly*, *Fiers v. Revel*, *Amgen [v. Chugai]*, or *Enzo Biochem*, require a re-description of what was already known." *Id.* (emphasis added). Applicants submit, as noted herein and as argued previously, kinases from yeast, mammals and *Drosophila* were easily identified and prepared, by those of ordinary skill in the at the time of filing of the present application. Thus, such proteins were well

known to those of ordinary skill in the art, and hence, a re-description of such proteins is not required under *Capon*. *Id.*

As set forth above, the present specification clearly provides written support for arrays comprising 50% of all expressed kinases of an organism, whether that organism is a yeast, a mammal or a *Drosophila*. Written description of an array comprising 122 kinases must necessarily provide sufficient description of an array comprising 61 kinases, regardless of the source of these kinases. *See Capon, id.* Therefore, Applicants respectfully submit that the present application discloses the full scope of the presently claimed invention. In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

In the Office Action at pages 6-12, the Examiner has rejected claims 1-11, 141, 164, 169, 173, 174, 177, 181-186, 188 and 193-195 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner contends that while the present specification is enabling for kinases from yeast, it does not provide sufficient enablement of an array comprising 61 kinases and functional kinase domains of mammal or *Drosophila*. The Examiner asserts that the presently claimed arrays encompass an enormous scope because the present claims do not place any limitations on the kind, number and/or length of kinase. Furthermore, the Examiner alleges that the specification does not provide any reasonable

assurance that the 61 kinases found in yeast could be found in mammals or *Drosophila*, and that it is not apparent from the specification whether the same number of kinases or the kind of kinases or functional domain thereof can be found in any other organisms and made into an array. Finally, the Examiner asserts that in a highly unpredictable art, such as biotechnology, one cannot predict from a single species its correspondence or extrapolation to the genus. The Examiner therefore concludes that the presently claimed invention is not enabled. Applicants respectfully disagree with the Examiner's contentions and conclusions.

As set forth in M.P.E.P. § 2164.01(a), there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 858 F.2d 731, 737, (Fed. Cir. 1988).

As acknoweldeged by the Examiner, the present specification clearly provides an enabling disclosure of arrays comprising yeast kinases. As discussed in Applicants' previous reply filed December 21, 2007, the use of kinases from other organisms, including mammals and *Drosophila*, in the arrays of the presently claimed invention, would not have required undue experimentation, but rather, simple, straightforward experiments. The protein kinases and functional kinase domains for use in the presently

claimed invention are all well-known, well-characterized proteins that the ordinarily skilled artisan would easily comprehend. For example, in *Hanks, S.K. and Hunter, T., FASEB J.*, 9:576-596 (1995) (cited as document U with the Office Action dated December 29, 2005), the authors state that, as of 1995, "there are now hundreds of different members [of the kinase superfamily] whose sequences are known." *Hanks and Hunter*, page 576. Furthermore, kinases, for example serine kinases, were already readily recognized in 1995 by virtue of their conserved subdomains. *Hanks and Hunter*, page 576 (abstract).

In the Office Action at page 8, the Examiner contends that, regardless of the disclosure of kinases in Hanks and Hunter, disclosure of kinases from mammals, *Drosophila*, or any other origin are not provided. Applicants respectfully submit that in addition to the disclosure provided in Hanks and Hunter, as discussed in detail in the Declaration of inventor Michael Snyder ("the Snyder Declaration") filed herewith, the protein kinases and functional kinase domains used in the positionally addressable arrays that form the basis of the present claims were, at the time the application was filed, all well-known, well-characterized proteins.

As set forth in the Snyder Declaration at pages 3-4, section 7, as discussed in Hunter and Plowman, "The protein kinases of budding yeast: six score and more," *TIBS 22:18-22* (1997) (cited in Applicants' 6th SIDS as NPL9; hereinafter "Hunter and Plowman"):

> [b]udding yeast has 113 conventional protein kinase genes, corresponding to ~2% of the total genes (see Table 1 in centrefold). More than 60% of these protein kinases have either known or suspected functions; the remainder are novel, and functional analysis awaits. In terms of defined functions encoded by the yeast

> genome, protein kinases come in a close second behind transcription factors.

Hunter and Plowman at page 18, first column, first paragraph. In addition, a review by Manning *et al.*, "The Protein Kinase Complement of the Human Genome," Science 298:1912-1934 (2002) (cited in Applicants' 6th SIDS as NPL13; hereinafter "Manning1"), indicates that "[p]rotein kinases are among the largest families of genes in eukaryotes and have been intensively studied." Manning1 at page 1913, first column, first paragraph.

As set forth in the Snyder Declaration at pages 4-5, sections 8 and 9, it was well recognized at the time of filing that kinases are highly conserved such that homologs exist between yeast and many other organisms. Furthermore, the regulation of the different kinases and the phosphorylation motifs of substrates recognized by related kinases are often the same, indicating that they behave similarly biochemically. As set forth in Manning *et al.*, "Evolution of protein kinase signaling from yeast to man," *TRENDS in Biochemical Sciences 27*:514-520 (2002) (cited in Applicants' 6th SIDS as NPL12; hereinafter "Manning2"):

> all major kinase groups and most kinase families are shared among metazoans, and many are also found in yeast, reflecting the breadth of conserved function mediated by kinases. This ancient conservation enables cross-species analysis of function, particularly of human kinases in simpler model systems. Of 209 subfamilies, 51 are present in all four genomes, and 144 are present in all metazoans, indicating that most divergence of kinases into specific functions and families occurred during early eukaryotic and metazoan evolution.

Manning2 at page 514, second column, first full paragraph, and at Figure 1 and Table 1. This known relationship is also addressed in Manning 1:

> Phylogenetic comparison of the human kinome with that of yeast, worm, and fly confirms that most kinase families are shared among metazoans and defines classes that are expanded in each lineage. Of 189 subfamilies present in human, 51 are found in all four eukaryotic kinomes, and these presumably serve functions essential for the existence of a eukaryotic cell. An additional 93 subfamilies are present in human, fly, and worm, implying that these evolved to fulfill distinct functions in early metazoan evolution. Comparison with the draft mouse genome indicates that more than 95% of human kinases have direct orthologs in mouse; additional orthologs may emerge as that genome sequence is completed.

Manning1 at page 1914, last paragraph bridging first and second columns. *See also* Hunter and Plowman at page 20, second column, second paragraph, "[m]ost of the main vertebrate subfamilies of protein kinases are represented in yeast."

Furthermore, as discussed in the Snyder Declaration at page 5, section 9, as function is often highly conserved, human kinases can be substituted for yeast kinases, illustrating the highly conservative nature of these proteins. *See* Lee and Nurse, "Complementation used to clone a human homologue of the fission yeast cell cycle control gene cdc2," *Nature 327*: 31-35 (1987) (cited in Applicants' 6th SIDS as NPL10; hereinafter "Lee and Nurse"):

> Because the human CDC2Hs gene can provide all of the functions of cdc2Sp in fission yeast it is reasonable to assume that it performs a similar role to cdc2Sp in controlling the human cell cycle. This conclusion is supported by the structural similarity between the two genes both in overall homology and size of the proteins. . . .
>
> The identification of a cdc2-like function in human cells suggests that elements of the mechanisms by which the cell cycle is controlled will probably be found in all eukaryotic cells.

Lee and Nurse at page 35, first column to second column.

It was even acknowledged and accepted by Examiner Tran in the Office Action dated July 31, 2006, that "the large protein kinase superfamily are well characterized and known in the art such that the sequence of *any* kinases from *any* mammal, yeast and Drosophila can be determine[d] by bioinformatics tools and publicly available sequence information." Office Action at page 7, lines 4-7 (emphasis added). A person of ordinary skill in the art would readily recognize that any of the well known and characterized kinases, from any organism, could easily be utilized in the preparation of the presently claimed positionally addressable arrays. Therefore, at the time this application was filed, the "state of the art" in protein kinases was such that a person of ordinary skill in the art would have readily recognized from the present specification, and the knowledge available in the art, that kinases of yeast, mammals and *Drosophila* could be utilized to practice the presently claimed invention.

Applicants respectfully submit that methods that could be used to confirm kinase activity were well known as of the filing date of the present application (*see e.g.*, Example 1 of present specification). *See also* Snyder Declaration at pages 3-4, section 7. Thus protein kinases, and functional kinase domains thereof, were well-known in the art at the time of filing the present application. The Examiner contends, however, that the present specification does not provide methods by which identification of other kinases beyond yeast kinases have been identified. Applicants respectfully submit that the present claims are not directed to the *identification* of kinases of the recited organisms, but rather to preparation of positionally addressable arrays *comprising* these kinases. The Examiner is reminded that, in order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary

skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (CCPA 1981). Furthermore, "every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification," rather, what is needed is "reasonable detail" in order to enable members of the public to understand and carry out the invention. *Genetech, Inc. v. Novo Nordisk, A/S*, 103 F.3d 1361, 1366 (Fed. Cir. 1997).

Applicants submit that the state of the art in protein kinases at the time of filing of the present application was such that the ordinarily skilled artisan, possessing a typical level of skill in protein purification and analysis, would have readily recognized that the kinases of mammals, yeast and *Drosophila* were well known, and/or could be readily identified. The presently claimed invention recites a positionally addressable array which comprises 61 purified active kinases or functional kinase domains of a mammal, 61 purified active kinases or functional kinase domains of a yeast or 61 purified active kinases or functional kinase domains of a *Drosophila*. Contrary to the Examiner's assertion at pages 9-10 of the Office Action, the presently claimed invention does not require the arrays to comprise the *same* 61 kinases, or combinations of kinases from different organisms, but rather, to simply comprise 61 purified active kinases (or functional domains) of these organisms. As noted above, and as detailed in the Snyder Declaration at pages 3-5, sections 7-9, it was well within the ability of the ordinarily

skilled artisan at the time of filing of the present application to identify which proteins of a mammal, yeast or *Drosophila* were protein kinases or functional kinase domains thereof, and prepare an array comprising 61 of these purified active kinases or functional domains.

As noted above, other factors that are to be considered when determining whether the claims are enabled by the specification are the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Applicants note that the present specification clearly provides numerous examples of methods for preparing the presently claimed positionally addressable arrays utilizing yeast protein kinases (*see e.g.*, specification at pages 27-38; see also, Snyder Declaration at pages 6-7, sections 11 and 12). Based on knowledge available in the art at the time of filing, specifically, the ability to identify and prepare purified protein kinases from yeast, mammals and *Drosophila,* the highly conserved nature of the proteins (*see* Snyder Declaration), and the detailed directions provided in the present specification, it would not have required undue experimentation to prepare arrays comprising kinases from any of these organisms.

The Examiner contends that, as the field of biotechnology is highly unpredictable, one cannot determine whether the generation of arrays comprising kinases of one organism (yeast) would be predictive of arrays comprising kinases of mammals or *Drosophila.* The Examiner points to Applicants' comments regarding the unpredictability in the art at the time of filing of the application, and contends that these

statements provide evidence as to the high unpredictability in the art, and thus, disclosure of a single species of protein would not be enabling for the broad scope of other proteins.

Regarding these assertions, the Examiner is reminded that the present claims are directed to positionally addressable arrays, *not* proteins. The present specification provides detailed methods for attaching kinases or functional kinase domains to the surface of a solid support (e.g., polydimethylsiloxane), for example, through the use of a 3-glycidooxypropyltrimethyoxysilane linker (GPTS). Applicants submit that the source or even identity of the kinase would not have any effect on the ability to attach the proteins to the surface of a solid support. The fact that a yeast kinase can be attached in this manner would clearly provide sufficient guidance to a person of ordinary skill in the art to utilize the same methods for attaching a kinase from a mammal or *Drosophila*, as discussed in the Snyder Declaration at pages 6-7, section 12.

Applicants agree with the Examiner that, prior to the disclosure of the present application, it was highly unpredictable to prepare positionally addressable arrays comprising purified active kinases. It is only after the detailed disclosure of such methods in the *present specification* that such arrays could have been produced, as has been clearly demonstrated in the present specification. However, once these methods were provided, the ability to utilize these same methods to attach kinases from organisms beyond yeast was clearly not unpredictable. The Examiner is reminded that the test of enablement is not whether *any* experimentation is necessary, but whether, if experimentation is necessary, it is *undue*. *See* M.P.E.P. § 2164.01 (emphasis added). Applicants submit that at most, only minor, routine experimentation would be required to prepare arrays of mammalian or *Drosophila* kinases or functional kinase domains. As

noted above, kinases from yeast, mammals or *Drosophila* were easily identified and generated at the time of filing of the present application. Utilizing the detailed guidance provided in the present specification for attaching yeast kinases to a solid support, a person of ordinary skill in the art, with only routine experimentation, would have been able to prepare positionally addressable arrays comprising 61 purified active kinases or functional kinase domains thereof, any of the recited yeast, mammal or *Drosophila* organisms.

Accordingly, Applicants submit the present specification clearly enables the presently claimed invention. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Rejection Under 35 U.S.C. § 102(a), or 35 U.S.C. § 103(a), Over Uetz

In the Office Action at pages 13-16, the Examiner has rejected claims 1-11, 141, 181-186, 188 and 193-195, as allegedly being anticipated by, or in the alternative, as allegedly being obvious in view of, Uetz *et al.*, *Nature 403*:623-631 (February 10, 2000) (hereinafter "Uetz"). Applicants respectfully traverse this rejection.

The Examiner contends that Uetz discloses a protein array comprising yeast genome encoded proteins, and that the proteins were expressed in 96-well plates. The Examiner asserts that the claimed kinase would have been inherent to the yeast array disclosed in Uetz, since yeast inherently contain kinase in their structure, or that they would have been obvious to determine given the identified genome of yeast. Applicants respectfully disagree with the Examiner.

Present claim 1 (and hence, claims 2-11, 141, 181-186, 188 and 193-195 that depend ultimately therefrom) recites a positionally addressable array comprising 61 *purified active* kinases or functional kinase domains thereof at a recited density. Applicants respectfully submit that Uetz does not disclose the preparation of an array comprising *purified active* kinases, and hence, cannot anticipate the presently claimed invention.

As discussed in Applicants' reply of December 21, 2007, the Methods section of Uetz, at page 627, discloses that the arrays were prepared by transferring patches of transformed yeast cells into wells of a micro-array assay plate. Uetz does not disclose *any purification* of the yeast proteins prior to placement in the assay plate, just simply transfer of the transformed cells. Hence, Uetz does not disclose the use of *purified* kinases or functional kinase domains, as recited in present claim 1. As set forth in M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Thus, as Uetz does not disclose each and every element of present claim 1, it cannot and does not anticipate the presently claimed invention.

On pages 15-16, the Examiner has responded to Applicants' previous remarks regarding the fact that the presently claimed positionally addressable arrays comprise purified active kinases (or functional kinase domains) by merely removing these limitations from the claims. The Examiner states "[t]he claims are not drawn to a process or [sic] preparing an array, as argued. Rather to an array (product) itself." Office Action at page 15, paragraph 2. In addition, the Examiner states "it is immaterial

as to whether the product in the array is pure or not as much as the array is taught and known in the art." *Id.* at page 16, lines 3-6.

Applicants respectfully disagree with the Examiner. While the presently claimed invention is indeed directed to an array (product), this product must comprise kinases (or kinase domains) that are *purified and active*. This is not a process limitation, but rather a *characteristic of the components of the array*. Stating that "it is immaterial as to whether the product in the array is pure or not" completely reads an element out of the present claims that defines characteristics of the array. While claims are to be given their broadest reasonable interpretation (*see* M.P.E.P. § 2111), the Examiner is reminded that each element in a claim is deemed material to defining the scope of the invention (*see Waner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 US 17, 41 (1997), and reading out an express limitation is not allowed (*see Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993)). Thus, as Uetz does not disclose arrays comprising *purified* kinases or functional kinase domains, clearly a required element of the claims, it cannot and does not anticipate the presently claimed invention.

With regard to the Examiner's assertion that Uetz renders obvious the presently claimed invention, Applicants note that, even assuming the arrays disclosed in Uetz comprise 61 kinases, there is no disclosure in Uetz sufficient to render obvious the construction of an array of 61 kinases or functional kinase domains, in which the array comprises kinases that are *purified and active*, as recited in present claim 1.

As reaffirmed by the U.S. Supreme Court, courts are "to look at any secondary considerations that would prove instructive," when considering the obviousness of an invention. *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (April 30, 2007). For

example, as set forth in M.P.E.P. § 2141(III), objective evidence or secondary considerations such as unexpected results and the skepticism of experts is relevant to the issue of obviousness and must be considered in every case in which they are present. Furthermore, as noted in M.P.E.P. § 2143.02, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048 (CCPA 1976).

As noted in the December 21, 2007 reply, at the time of filing of the present application, it was unexpected that kinases and functional kinase domains of these kinases could be purified and placed on a solid support to form an array, and that these kinases and kinase domains *would retain their kinase activity*. As detailed in the Snyder Declaration, it is only after the guidance provided in the present specification that a person of ordinary skill in the art would consider it possible to generate the presently claimed arrays. As noted in the Snyder Declaration at pages 7-8, section 13, artisans in the field, before and even well after the time the present application was filed, thought that proteins in arrays, such as those used to prepare the arrays of the presently claimed invention, would denature and therefore be inactive. It was an unexpected and surprising result that the purified proteins on the arrays of the presently claimed invention retained their activity and could be utilized to determine meaningful biological interactions between the purified, active kinases and their targets (such as enzyme-enzyme or enzyme-substrate interactions). Applicants respectfully submit that, it is only after the guidance provided in the present specification that a person of ordinary skill in the art would consider it possible to generate the presently claimed arrays.

As discussed in the Snyder Declaration at pages 8-11, sections 14-19, the following exemplary references describe the skepticism from those in the field regarding the preparation of protein arrays both before and after the time of filing of the present application, as well as some of the problems regarding preparation of protein arrays comprising large numbers of purified active proteins that were overcome by the presently claimed invention.

For example, Anderson, K.S. and LaBaer, J., *Journal of Proteome Research 4*:1123-1133 (March 30, 2005) (copy provided as Exhibit A with Applicants' Reply to Office Action dated December 21, 2007; hereinafter "Anderson and LaBaer") state that:

> [t]heir theoretical advantages notwithstanding, protein microarrays have still not found widespread use, in part because producing them is challenging. Historically, it has required the high-throughput production and purification of protein, which then must be spotted on the arrays. Once printed, concerns remain about the shelf life of proteins on the arrays.

Anderson and LaBaer, page 1129. In addition, Shaw, G., *Drug Discovery and Development* (February 3, 2005) (copy provided as Exhibit B with Applicants' Reply to Office Action dated December 21, 2007; hereinafter "Shaw") states that:

> "[i]t was first thought that protein biochips would just be an extension of DNA microarrays, and that hasn't exactly panned out," says Bodovitz. That's because proteins have proven to be much trickier to work with in array format than their genomic counterparts. First of all, there are issues of stability. Membrane proteins, for example, make up the majority of potential drug targets, but they're particularly challenging to stabilize. Then there's the choice of immobilization technique, which determines how well the target protein presents itself to the capture agent, and the problem of nonspecific binding. And of course, proteins are inherently unstable outside their natural habitat of living cells, making them much more challenging than DNA to tag and manipulate.

Shaw at page 1.

In addition, as discussed in the Snyder Declaration and in the following references, it was well known in the art at the time of filing the present application that spotting proteins on solid surfaces often resulted in protein denaturation caused by uncontrolled adsorption, thereby inactivating the proteins. *See* Abstract of both Tleugabulva *et al.*, "Evidence for the denaturation of recombinant hepatitis B surface antigen on aluminum hydroxide gel," *J. Chromatogr. B. Biomed. Sci.* 702:153-163 (1998) (cited in Applicants' 6th SIDS as NPL16); and Servagent-Noinville *et al.*, "Conformational Changes of Bovine Serum Albumin Induced by Absorption on Different Clay Surfaces: FTIR Analysis," *J. Colloid Interface Sci*, 221:273-283 (2000) (cited in Applicants' 6th SIDS as NPL15).

Thus, as noted in the references cited above, Applicants respectfully submit that prior to the filing of the present application, experts in the field were clearly skeptical of the ability to prepare protein arrays comprising purified active enzymes. In response to Applicants' arguments, the Examiner asserts that obviousness does not require absolute predictability, and asserts that as kinases were known at the time of filing, placing them on an array would have been obvious to one of ordinary skill in the art. Applicants note that the Examiner appears to be trying to have it both ways, now appearing to *agree* with Applicants that in fact, kinases of the various organisms such as mammals, *Drosophila* and yeast were well known at the time of filing the application. This is in stark contrast to the Examiner's contrary position noted above with regard to written description and enablement of the presently claimed invention.

While Applicants agree that kinases of *Drosophila*, yeast and mammals were well known in the art at the time of filing the present application, it would not have been obvious to place these kinases on a positionally addressable array so that they were not only *purified*, but also *active*. As discussed in the Snyder declaration at pages 9-13, sections 18-23, and in the references cited therein and below, prior to the presently claimed invention, only small numbers of proteins, and/or inactive proteins, at low densities, were able to be displayed on an array. It is only after the teachings of the present application that large numbers of purified proteins were able to be placed on a solid support, in the recited density, such that they remained active.

For example, as discussed in Bussow *et al.*, "A method for global protein expression and antibody screening on high-density filters of an arrayed cDNA library," *Nucleic Acids Res. 26*: 5007-5008 (1998) (cited in Applicants' 6th SIDS as NPL3; hereinafter "Bussow1"), large scale protein arrays were produced, but only using denatured (and thus inactive) proteins. ("These protein filters were processed on pre-soaked blotting paper, i.e., denatured in 0.5 M NaOH, 1.5 M NaCl for 10 min, neutralized for 2x5 min in 1 M Tris-HCl, pH 7.5, 1.5M NaCl and incubated for 15 min in 2x SSC. Filters were air-dried an stored at room temperature." Bussow1 at page 507, second column, first paragraph.) Similarly, in Bussow *et al.*, "A human cDNA library for high-throughput protein expression screening," *Genomics 65*:1-8 (2000) (cited in Applicants' 4th SIDS as C9; hereinafter "Bussow2"), denaturing conditions were used to prepare the protein arrays. ("Twenty-five microliters of 50% Ni-NTA agarose was added to protein extracts obtained under denaturing conditions." Bussow2 at page 2, first column, third paragraph.) In addition, in the introduction of Bussow2, the authors

discuss the difficulties in producing large amounts of purified proteins and maintaining their activity when placed on an array:

> the individuality of protein molecules demands highly customized procedures for their expression. Automation of these procedures requires systems that allow the efficient handling of large numbers of clones representing many different proteins. Bacterial systems are easy to manage but the expression of eukaryotic proteins can be problematic, due to aggregation, formation of insoluble inclusion bodies, and/or degradation of the expression product. Eukaryotic systems suffer from lower yields of heterologous protein (e.g. Saccharomyces cerevisiae), high demands on sterility (e.g mammalian systems) or time consuming cloning procedures (e.g. Baculovirus system).

Bussow at page 1, last paragraph bridging first and second columns (citations emitted, emphasis added). Thus, rather than attempt to overcome these various issues, the authors proceeded to produce denatured proteins in *E. coli* for use in their arrays. Similarly, Lueking *et al.*, "Protein microarrays for gene expression and antibody screening," *Anal. Biochem. 270*:103-111 (1999) (cited in Applicants' 6th SIDS as NPL11; hereinafter "Lueking"), also prepared protein arrays utilizing denaturing conditions (6M guanidinium-HCl, 0.1M NaH2PO4, 0.01 M Tris-HCl, pH 8.0, Lueking at page 104, second column, first paragraph).

In Ge, "UPA, a universal protein array system for quantitative detection of protein-protein, protein-DNA, protein-RNA and protein-ligand interactions," *Nucleic Acids Research 28*:e3(i-vii) (2000) cited in Applicants' 6th SIDS as NPL6; the author was only able to produce arrays comprising 48 proteins at a very low density, utilizing a traditional purification format. Extension of this disclosure to arrays comprising at least 100 different substances per cm^2 would have required extensive, undue experimentation beyond the scope of the disclosure provided in this reference.

Thus, as noted in the references cited above, Applicants respectfully submit that those of skill in the art were clearly skeptical of the ability to prepare protein arrays comprising large numbers of purified, active enzymes, at the densities recited in the presently claimed invention. Instead, denaturing conditions or traditional purification methods on small numbers of proteins were required.

Absent the teachings of the present application, there was no reasonable expectation that arrays comprising at least 100 different substances per cm^2, wherein the substances comprise 61 purified, active kinases on a solid support, could be successfully prepared, at the time of filing of the present application. It is only after the guidance of the present specification, specifically the methods described in the present application which allowed for large-scale purification and arraying of active kinases or functional kinase domains, that preparation of the presently claimed positionally addressable arrays was possible. The methods of the presently claimed invention, as discussed below and in the Snyder Declaration, are suitable for rapidly purifying large numbers of samples, such as the purification of active kinases isolated from mammalian, yeast, and *Drosophila*. As an example, kinases were purified by growing different strains of pep4 yeast cells, each containing a plasmid encoding a single GST-tagged kinase gene, in 96-well plates. Galactose was added to induce protein expression. The cultures of the same strain were combined, washed, resuspended and lysed. The GST fusion proteins were purified from these strains using glutathione beads and standard protocols in a 96-well format. This method allowed for the purification of a high number of yeast kinases in a relatively short amount of time. The buffers and methods used also ensured that the purified

kinases or functional kinase domains retained their activity. *See* Example 1 of the present specification at page 26, line 25, through page 27, line 19.

Positionally addressable arrays were then prepared using the purified, active proteins purified as described above. Arrays were made from polydimethylsiloxane (PDMS) (Dow Chemical, USA), which was cast over microfabricated molds. Liquid PDMS was poured over the molds and, after curing flexible silicone elastomer array sheets were then peeled from the reusable molds. Arrays were immersed in 3-glycidooxypropyltrimethoxysilane linker (GPTS) in order to facilitate adsorption of protein to the wells. To attach proteins to the chips, protein solutions were added to the wells and incubated on ice for 1 to 2 hours. After rinsing with cold HEPES buffer, the wells were blocked with BSA in PBS. *See* Example 1 of the present specification at page 27, line 21, through page 28, line 9.

As discussed above and throughout the Snyder Declaration, extending these methods to the preparation of arrays comprising purified active kinases from mammals and *Drosophila* was well within the level of the ordinarily skilled artisan and would not have required undue experimentation. Applicants respectfully submit that the methods set forth in the present application are sufficient to enable a person of ordinary skill in the art to make and use positionally addressable arrays comprising 61 purified, active kinases of yeast, mammals and *Drosophila*. However, such methods were only available as a result of the filing of the present application. It is only after the disclosure of the present methods that such arrays could be produced. The presently claimed invention is not simply a positionally addressable array comprising kinases, but rather, an array that comprises *purified active* kinases. There is no reasonable expectation of success that

arrays of this type existed, or could have been produced, based on the disclosure of Uetz. Thus, Applicants respectfully submit that the presently claimed invention cannot be rendered obvious by the disclosure of Uetz.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(a) and 35 U.S.C. § 103(a), over Uetz.

Rejection Under 35 U.S.C. § 103(a) Over Shalon, In View of Felder or Lafferty

In the Office Action at pages 16-20, Examiner has rejected claims 1-11, 141, 164, 169, 173, 174, 177, 181-186, 188 and 193-195 under 35 U.S.C. § 103(a), as allegedly being upatentable over Shalon (WO 95/35505; hereinafter "Shalon") in view Felder *et al.* (U.S. Patent No. 6,458,533; hereinafter "Felder") or Lafferty (U.S. Patent No. 6,972,183; hereinafter "Lafferty"). Applicants respectfully traverse this rejection.

The Examiner contends that Shalon discloses a microarray having regions with a density of at least about $100/cm^2$, and that the arrays can comprise enzymes. The Examiner notes, however, that Shalon does not disclose arrays comprising kinases. The Examiner relies on the disclosures of Felder or Lafferty to cure this deficiency. Specifically, the Examiner contends that Felder discloses that kinases are enzymes, and Lafferty discloses an array containing substrate-enzymes, such as kinases. The Examiner therefore concludes that it would have been obvious to prepare the array disclosed in Shalon using the kinases disclosed in Felder and Lafferty, and hence, the presently claimed invention is rendered obvious. Applicants respectfully disagree with the Examiner's contentions and conclusions.

As stated in Applicants' reply of December 21, 2007, and as discussed in the Snyder Declaration at pages 13-14, section 26, Shalon is primarily directed to arrays comprising polynucleotides (*see* Examples 1-3), and only mentions in passing that arrays comprising proteins and enzymes could be constructed. Furthermore, Felder discloses preparation of arrays comprising peptides that are *substrates* for kinases, not arrays comprising the kinases themselves: "[a] chimeric linker molecule is prepared in which a 25 base pair oligonucleotide complementary to one of the anchors is crosslinked to a *peptide substrate of a tyrosine phosphokinase enzyme*." Felder at column 44, lines 18-21 (emphasis added). Thus, Felder does not disclose the preparation of arrays comprising 61 purified active kinases or functional kinase domains thereof, as recited in present claim 1.

With regard to Lafferty, Applicants note that the arrays disclosed therein are limited to enzymes expressed in expression library cells, and that Lafferty does not disclose the purification of these enzymes prior to placement on a solid support, as recited in the presently claimed invention. As discussed in the Snyder Declaration, as set forth in Lafferty, at column 18, lines 1-14:

> The library comprises a plurality of recombinant clones, which comprise host cells transformed with constructs comprising expression vectors into which have been incorporated nucleic acid sequences derived from the DNA samples. One or more substrates and at least a subset of the clones is then introduced, either individually or together as a mixture, into capillaries (all or a portion thereof) in a capillary array. Interaction (including reaction) of the substrate and a clone expressing an enzyme having the desired enzyme activity produces an optically detectable signal, which can be spatially detected to identify one or more capillaries containing at least one signal-producing clone. The signal-producing clones can then be recovered from the identified capillaries.

Applicants respectfully submit, therefore, that Lafferty does not disclose arrays comprising 61 purified active kinases, as set forth in the presently claimed invention.

In view of the foregoing remarks, and those in the Snyder Declaration at pages 13-15, Applicants respectfully submit that Shalon, Felder and Lafferty, alone or in combination, do not disclose the presently claimed positionally addressable arrays, specifically, arrays comprising 61 purified active kinases or functional kinase domains thereof, as set forth in present claim 1. Specifically, the references cited by the Examiner do not disclose arrays comprising purified active kinases, as recited in present claim 1. Thus, Applicants submit that the Examiner has not set forth a *prima facie* case of obviousness, as there are clearly differences between the cited references and the presently claimed invention that have not been addressed by the Examiner.

In response to Applicants' arguments, the Examiner continues to assert that Felder discloses an array of proteins, and as kinases of the recited organisms were known in the art at the time of filing, it would have been obvious to construct the presently claimed arrays. Applicants respectfully disagree with the Examiner.

As set forth in detail above, and throughout the Snyder Declaration, Applicants respectfully submit that there was no reasonable expectation of success of preparing an array comprising 61 *purified active* kinases or functional kinase domains of these kinases, based on the references cited by the Examiner. Applicants respectfully submit that, at the time of filing of the present application, experts in the field were skeptical, and it was unexpected, that arrays of purified kinases and functional kinase domains of these kinases could be prepared, and that these proteins would retain their enzymatic activity on the arrays. It was also unexpected that these positionally addressable arrays

could be used to determine meaningful biological interactions (such as enzyme-enzyme or enzyme-target interactions) between the purified active kinases and their targets. It is only by following the guidance of the present specification that a person of ordinary skill in the art would be able to generate the presently claimed arrays.

As discussed above and in the Snyder Declaration, Applicants respectfully submit that at the time of filing of the present application, it was unexpected that kinases and functional kinase domains of these kinases could be purified and placed on a solid support to form an array. It was also unexpected that the purified kinases and functional kinase domains of these kinases would retain their activity when placed onto the array.

As set forth in the Snyder Declaration, it is only after the guidance provided in the present specification that a person of ordinary skill in the art would consider it possible to generate the presently claimed arrays. Thus, prior to the filing of the present application, there was no reasonable expectation of success of preparing an array comprising 61 purified active kinases or functional kinase domains of these kinases. At the time of filing of the present application, experts in the field were skeptical, and it was unexpected, that purified kinases and functional kinase domains of these kinases could be placed on a solid support to form an array, and that these proteins would retain their activity.

Therefore, in view of the foregoing remarks, and those in the Snyder Declaration, Applicants respectfully submit that the disclosures of Shalon, Felder and Lafferty, alone or in combination, cannot render obvious the presently claimed invention. Hence, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

Double Patenting Rejection

In the Office Action at pages 20-21, the Examiner has provisionally rejected claims 1-11, as allegedly being upatentable under judicially created doctrine of nonstatutory double patenting (ODP), in view of copending Application No. 10/477,329 (hereinafter "the '329 Application"). Applicants respectfully traverse this rejection.

The priority date of the '329 application is May 11, 2001, whereas the priority date of the present application is May 4, 2000. Applicants note that the priority date of the '329 reference application used in making this obviousness-type double patenting rejection is after the priority date of the present application. Hence, the present application is "the earlier filed application of the two pending applications" as that phrase is meant in MPEP § 1490.V.D. Applicants believe that the arguments presented herein will place the present application in condition for allowance except for the ODP rejection. Thus, Applicants request the Examiner to hold this rejection in abeyance until the arguments herewith have been considered, and to reconsider and withdraw this rejection upon allowance of the present claims in accordance with MPEP § 1490.V.D.

Conclusion

All of the stated grounds of rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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